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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/519,959	03/07/2000	Nancy Carrasco	96700/488	9663

7590 06/04/2002

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
09/519,959			

EXAMINER	
ART UNIT	PAPER
	15

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Commissioner of Patents and Trademarks

Advisory Action	Application No.	Applicant(s)	
	09/519,959	CARRASCO ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 April 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *12 April 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☒ they raise the issue of new matter (see Note below);

(c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-11*.

Claim(s) withdrawn from consideration: _____.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *See the attached Note of Explanation*

NOTE OF EXPLANATION

1. The amendment filed April 12, 2002 in Paper No. 14 is acknowledged, but will not be entered for the following reasons:

(a) The proposed amendment will not be entered because entry of the amendment would have raised new issues that would have required further consideration and/or search. In particular, further consideration would have been required to determine if the amendment to claim 1 would have obviated the grounds of rejection of claims 1 and 2 under 35 USC § 102(b). Notably, although Applicants assert that recitation of the limitation requiring the use of an agent that "specifically and selectively binds to mgNIS" distinguishes the claimed invention from the prior art cited as the basis of the rejection under 35 USC § 102(b), further search and consideration would have been necessary to determine that the agents of the prior art, namely radioiodide and ^{99m}Tc-pertechnetate, do not bind to mgNIS, since it seems likely that radioiodide and ^{99m}Tc-pertechnetate would interact with mgNIS, and might conceivably bind to mgNIS, albeit perhaps only transiently.

In traversing the grounds of the rejection of the claims under 35 USC § 103(a), Applicants have asserted that Cancroft, et al "merely suggests a method of providing confirmatory evidence of the presence of breast cancer in those cases already identified by standard diagnostic techniques" (page 5, paragraph 2) and that it would not have been obvious to one of ordinary skill in the art at the time the invention was made to have detected the presence of breast cancer in a subject by detecting the expression of mgNIS in the subject's breast, since Eskin, et al teaches that radioiodide is concentrated in carcinoma and dysplasia. Contrary to Applicants' remarks, however, the teachings of Eskin, et al would not have been construed as a suggestion that radioiodide is potentially more concentrated in normal breast tissue than in abnormal breast tissue, i.e., malignant, hyperplastic, or dysplastic cells (page 5, paragraph 4). In fact, Eskin, et al teach that the incidence of increased radioiodine by breast tissue uptake parallels abnormal breast tissue changes (abstract). Furthermore, Eskin, et al disclose, "[i]n these series, 5 cases of carcinoma were found" and "[i]n 2 of these, the

initial indicator of abnormality was the elevated radioiodine uptake" (page 401, column 2). This disclosure, contrary to Applicants' assertion, would have provided the suggestion that detecting abnormal breast tissue in a subject by measuring the expression of mgNIS, in turn, by measuring the level of radioiodide or ^{99m}Tc-pertechnetate uptake by the breast tissue, can, in fact, lead to the detection of malignant breast tissue in the subject, despite the fact that Eskin, et al teaches that non-malignant dysplastic tissue might also be detected in some subjects, as it is clinically prudent, if not imperative to identify *any* abnormality of the breast in order to "catch" as many malignancies as possible.

In their remarks, Applicants also refer to the teachings of Kilbane, et al; however, Kilbane, et al was not cited as part of the basis of the rejection of claims 1-11 under 35 USC § 112, second paragraph. This confusion has evidently arisen from an inadvertent typographical error in which "Kilbane, et al" was included in the first paragraph of the rejection, but it should be clear that since the Kilbane, et al was not properly cited, Kilbane, et al was not used as, or considered to be part of the basis of the rejection.

Nevertheless, in reply to Applicants' argument that the teachings of Kilbane, et al teach away from the claimed invention, since Kilbane, et al teach that NIS is expressed in both benign fibroadenomata and malignant breast carcinoma, evidence that NIS is expressed in atypical breast tissue, but not exclusively in malignant breast tissue, would not have dissuaded the artisan of ordinary skill from developing the invention. Atypical, dysplastic tissue is frequently at a pre-cancerous stage of development; such tissue may become malignant upon additional oncogenic change. Therefore, contrary to Applicants' assertion, it would appear that the teachings of Kilbane, et al would have provided the suggestion that determining the expression of mgNIS in breast tissue could be used to detect *pre-cancerous and early cancerous* lesions in the breast at a time before such lesions become malignant and one would have been motivated by the obvious advantage to the clinician and certain benefit to the patient that such a method might have offered.

Finally, Applicants have remarked that Cancroft, et al only teach that the method can be used in a confirmatory role since Cancroft, et al "did not look at patients that

were not known to have breast cancer" (page 5, paragraph 5). Accordingly, Applicants suggest that the claimed method for detecting breast cancer in a subject is distinguishable from the method of the prior art, since the method of the prior art merely teaches a method for confirming breast cancer. In reply to these remarks, it is noted that the claims are drawn to a method for detecting the presence of breast cancer in a subject *comprising* the step of determining whether or not mgNIS is expressed in the breast tissue; therefore, the practitioner of the claimed method would not be limited to practicing the step recited in the body of the claim, and it would have been obvious to one of ordinary skill in the art to acquire "confirmatory evidence of the presence of breast cancer in the subject" by another diagnostic means, rather than to rely merely upon the determination of expression of mgNIS in the subject's breast tissue as the sole criterion for a diagnosis of breast cancer. As such, it is not apparent that the claimed invention is not also "merely confirmatory", since it is not apparent that the practicing the step recited in the claim, and none other, could be, or would have been used to procure a definitive diagnosis of breast cancer. Nevertheless, the study of Cancroft, et al was conducted according to acceptable scientific standards, which included both positive and negative controls. The study included subjects that were suspected as having abnormal breast tissue, i.e., abnormal masses, some of which had presented with masses thought to be benign, fibrocystic disease. These subjects can be considered the "negative controls", and in fact, Cancroft, et al disclose a failure to detect focal concentrations of ^{99m}Tc-pertechnetate in the affected breast of these subjects, which suggests that the technique can distinguish benign lesions from malignant lesions (page 443, column 2). Other subjects included in the study that presented with masses thought to be malignant on mammography, which can be considered the "postive controls", had readily observable focal concentrations of ^{99m}Tc-pertechnetate on scintigraphy, which suggests the technique can distinguish normal tissue from malignant lesions (page 443, column 1). More strikingly yet, Cancroft, et al disclose that in one subject, one breast, which was thought to be unaffected on mammography, was found to have slightly increased uptake of ^{99m}Tc-pertechnetate on scintigraphy, which upon biopsy and pathological analysis was revealed as lobular hyperplasia approaching

lobular carcinoma *in situ* (page 443, column 1). This latter disclosure, in particular, would have suggested to the artisan that the method of Cancroft, et al can be a powerful diagnostic tool for detecting and localizing malignant and pre-malignant breast cancer in a subject.

In summary, Applicants' arguments have been carefully considered, but contrary to Applicants' assertion, the prior art does not teach away from the claimed invention, but rather would have provided suggestion and motivation to the artisan of ordinary skill at the time the invention was made to detect breast cancer in a subject by measuring the expression of mgNIS in the subject's breast tissue according to the method taught by Cancroft, et al, or according such a method modified in view of the teachings of Eskin, et al, Spitzweg, et al, and Jhiang, et al. Moreover, the artisan of ordinary skill in the art would have had a reasonable expectation of success in practicing such methods to detect breast cancer in a subject, as there is no evidence of record to support the contrary.

(b) The proposed amendment will not be entered because entry of the amendment would have raised the issue of new matter. It would have been necessary to consider whether or not the specification would provide proper antecedent basis for recitation of the limitation in claim 1 requiring the use of an agent that "specifically and selectively binds to mgNIS" to detect the presence or absence of breast cancer in a non-lactating subject. It would appear that the originally filed claims would have at least provided implicit support for a claim drawn to "[a] method for detecting the presence or absence of breast cancer in a non-lactating subject"; nonetheless, it would have been necessary also to consider whether or not the specification would have provided proper antecedent basis for recitation of this new limitation, as opposed to the originally claimed method for diagnosis.

(c) The proposed amendment will not be entered because entry of the amendment would not placed the application in better form for appeal by materially reducing or simplifying the issues for appeal. Although Applicants' grounds of traversal of the rejection of claims 1-11 under 35 USC § 103(a) have been carefully considered, the arguments have not been found persuasive, and so the rejection of the claims under

35 USC § 103(a) would have been maintained despite entry of the amendment. Additionally, although the proposed amendment to claim 7 would have obviated the grounds of rejection of claims 7-9 under 35 USC § 112, second paragraph, since claim 7 would no longer recite the term "hybridizes", the amendment to claim 1 would not have obviated the remaining grounds of the rejection of claims 1-11 under 35 USC § 112, second paragraph, since claim 1, as it would have be amended, would still not have recited a positive process step that would have clearly related back to the preamble of the claim.

For each the reasons set forth above, entry of the proposed amendment filed April 12, 2002 (Paper No. 14) will not be made.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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slr
May 21, 2002